REMARKS

The Amendments

In order to advance prosecution, Applicants have amended claim 37 to recite "each purine nucleotide present in the first strand or second strand, or both the first strand and second strand of the siRNA molecule, is a 2'-O-methyl or 2'-deoxy purine nucleotide". Support for this amendment can be found, inter alia, at page 15, lines 10-12; page 17, lines 5-8; page 20 line 30 to page 21 line 9; page 38 line 24 to page 42 line 24. Claims 1, 2, 4-15, 18-20, 22, 25, 26, 28, 29, 31, 32, and 34-36 were previously canceled. Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

Information Disclosure Statement

The Office notes that Japanese Patent number JP828687 will not be considered because it is in Japanese. The Applicants have resubmitted the IDS with a notation that the abstract only is to be considered. Applicants respectfully request that the abstract be considered.

Claim Objection

Claim 37 is objected to for containing several periods. The claim has been amended to remove the extra periods. Applicants respectfully request withdrawal of the objection.

Rejection of Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 Under Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 stand as provisionally rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Appl. No. 10/861,060. While not in agreement with the Office Action on this rejection, Applicants, in the interest of

efficient prosecution of this application, will consider submitting a terminal disclaimer over U.S. Appl. No. 10/861,060 upon indication of allowable claims in the instant application.

Rejection of Claims 3, 21, 23, 24, 30, 33, and 37 Under 35 U.S.C. § 103(a)

Claims 3, 21, 23, 24, 30, 33, and 37 stand rejected as allegedly obvious over Tuschl *et al.* (US 2004/0259247), Driscoll *et al.* (WO 01/49844), GenBank Accession No. D31839 gene sequence, and Parrish *et al.* (2000) Molecular Cell, 6:1077-1087. Applicants respectfully traverse the rejection as it applies to the presently claimed invention.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143. -

The Applicants submit that the Office has not established a *prima facie* case of obviousness. In the present case, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at the presently claimed invention. As described below, Applicants submit that the cited art, especially the teachings of Tuschl, teach away from the presently claimed invention. Where prior art references teach away from the claimed invention, there can be no motivation to combine the references to arrive at the claimed invention, as is the case here. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

In the interest of expediting prosecution, Applicants have amended claim 37 to recite "each purine nucleotide present in the first strand or second strand, or both the first strand and second strand of the siRNA molecule, is a 2'-O-methyl or 2'-deoxy purine nucleotide". One of skill in the art would not have had any motivation to combine the cited references, nor would one of skill in the art have any reasonable expectation of success with such combination, based on the teachings of Tuschl (alone or in combination with the other cited references) in targeting

SNCA with siRNA molecules wherein "one or more pyrimidine nucleotides present in the first strand or second strand of the siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide and each purine nucleotide present in the first strand or second strand, or both the first strand and second strand of the siRNA molecule, is a 2'-O-methyl or 2'-deoxy purine nucleotide", as is presently claimed.

The Office Action acknowledges that "Tuschl teach that extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl will abolish RNAi activity" (*see,* Office Action at page 7). None of the other references, alone, or in combination, can remedy the effect of Tuschl in teaching away from the presently claimed invention. Tuschl is the only reference addressing chemically modified siRNAs having "extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl" nucleotides, and all the evidence it provides demonstrates that such modified siRNAs are inactive. None of the other references relied upon for chemical modifications relate to siRNA. Parrish teaches only chemically modified long dsRNA constructs of greater than 720 nucleotides in length. No reference or combination of references teach the combination of different modifications as is presently claimed, let alone a combination that involves extensive 2'-O-methyl or 2'-deoxy modification or purine nucleotides along with 2'-deoxy-2'-fluoro pyrimidine modifications. Accordingly, the ordinary artisan would have derived no level of assurance from any of the cited references (or any other reference known to Applicant) that similar modifications would result in active siRNA molecules, particularly when Tuschl teaches that extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl will abolish RNAi activity.

Finally, in contrast to the Office's assertions, there would have been no motivation to combine the teachings of Driscoll with the teachings of Tuschl and Parrish as the Office suggests. The Office argues that "it would have been obvious to one of ordinary skill in the art to use the cDNA sequence of GenBank Accession No. D31839 as suggested by Driscoll to generate short interfering RNA sequences, comprising 2'-fluoro modifications as taught by both Tuschl and Parrish, for inhibition of the human alpha-synuclein sequence represented by SEQ ID NO:311" (*see*, Office Action at page 9). However, Driscoll teaches long, expressed, inverted repeat constructs that have complementarity to D31839. Because Parrish teaches long dsRNA,

Tuschl is the only reference that teaches siRNA. As stated above, Tuschl teaches away from the present invention.

Current case law mandates that there must be a *specific* suggestion to combine the particular references to arrive at the claimed invention.

> When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *The need for specificity pervades this authority.*

In re Lee, 61 USPQ2d 1430, 1434 (Fed. Cir. 2002) (emphasis added); *see also In re Deuel*, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995) (stating that the prior art must suggest the particular form of the invention and how to make it; general guidance is insufficient); and *In re Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (stating the prior art "that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious").

The combination of a lack of a specific and identifiable suggestion to make the particular combination of Driscoll and Parrish with Tuschl, and the fact that Tuschl teaches away from the extensive use of 2'-O-methyl or 2'-deoxy modifications, leads to a lack of a reasonable expectation of success in practicing the presently claimed invention by one of skill in the art at the time the invention was made.

For the reasons set forth above, one of skill in the art would not have been motivated to incorporate the instantly claimed modifications into a siRNA molecule targeting SNCA SEQ ID NO:311 as is presently claimed; nor would one of skill in the art have had any reasonable expectation of success with such a combination. Therefore, Tuschl, Driscoll, GenBank Accession No. D31839, and Parrish, alone or in combination, do not render the present claims obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these teachings.

Rejection of Claims 16 and 17 Under 35 U.S.C. § 103(a)

Claims 16 and 17 stand rejected as allegedly obvious over Tuschl *et al.* (US 2004/0259247), Driscoll *et al.* (WO 01/49844), GenBank Accession No. D31839 gene sequence, and Parrish *et al.* (2000) Molecular Cell, 6:1077-1087, further in view of Matulic-Adamic (1999) and Ortigao *et al.* (1992) *Antisense Res. Dev.* 2:129-146. Applicants respectfully traverse the rejection as it applies to the presently claimed invention.

As explained above, Tuschl teaches away from the presently claimed invention because "Tuschl teach that extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl will abolish RNAi activity" (*see,* Office Action at page 7). None of the other references, alone, or in combination, can remedy the effect of Tuschl in teaching away from the presently claimed invention. Parrish teaches only chemically modified long dsRNA constructs of greater than 720 nucleotides in length. Driscoll teaches long, expressed, inverted repeat constructs that have complementarity to D31839. Matulic-Adamic teaches ribozyme technology, and Ortigao teach single stranded antisense technology. No reference or combination of references teach the combination of different modifications as is presently claimed, let alone a combination that involves extensive 2'-O-methyl or 2'-deoxy modification or purine nucleotides along with 2'-deoxy-2'-fluoro pyrimidine modifications. Accordingly, the ordinary artisan would have derived no level of assurance from any of the cited references (or any other reference known to Applicant) that similar modifications would result in active siRNA molecules, particularly when Tuschl teaches that extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl will abolish RNAi activity.

For the reasons set forth above, one of skill in the art would not have been motivated to incorporate the instantly claimed modifications into a siRNA molecule targeting SNCA SEQ ID NO:311 as is presently claimed; nor would one of skill in the art have had any reasonable expectation of success with such a combination. Therefore, Tuschl, Driscoll, GenBank Accession No. D31839, Parrish, Matulic-Adamic and Ortigao, alone or in combination, do not render the present claims obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these teachings.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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